ORIGINAL ARTICLE

Early chemotherapy de-escalation strategy in patients with advanced-stage Hodgkin lymphoma with negative positron emission tomography scan after 2 escalated BEACOPP cycles

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KEY WORDS

BEACOPP, de-escalation, Hodgkin lymphoma, positron emission tomography, toxicity

ABSTRACT

INTRODUCTION Escalated BEACOPP (escBEACOPP: bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone) significantly improves overall response rates (ORRs) and prolongs progression-free survival (PFS) in patients with advanced-stage Hodgkin lymphoma (HL). However, 6 to 8 cycles of escBEACOPP are associated with increased acute toxicity and late complications.

OBJECTIVES We aimed to determine the role of early positron emission tomography–computed tomography (PET-CT) response assessment in a de-escalation strategy.

PATIENTS AND METHODS We retrospectively analyzed 188 consecutive patients with advanced-stage HL treated at diagnosis. Patients received 2 cycles of escBEACOPP followed by an early PET-CT response assessment performed after 2 cycles of chemotherapy (PET2). Patients with an active disease continued therapy with escBEACOPP, while those with negative PET2 were de-escalated to ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine). Radiotherapy was allowed in patients with stage IIBX.

RESULTS PET2 allowed for de-escalation of therapy in 141 patients (75%). Their ORR was 92.2%, with a complete remission (CR) rate of 91.5%; 10-year PFS and overall survival (OS) were 87.2% and 95%, respectively. In the whole cohort, ORR was 87.8% (CR, 85.6%), while the 10-year PFS and OS were 79.3% and 89.4%, respectively. Hematological and thromboembolic complications were significantly more frequent in patients treated with 6 escBEACOPP cycles, including febrile neutropenia (25 patients, [53.2%] vs 7 [5%]), serious anemia (35 [74.5%] vs 11 [7.8%]), or thrombocytopenia (16 [34%] vs 7 [5%]) (P <0.001 for all comparisons with de-escalation strategy) as well as pulmonary embolism (3 [6.4%] vs 0) (P = 0.02).

CONCLUSIONS The early de-escalation strategy allows for effective treatment of advanced HL, with a comparable efficacy to that of 6 to 8 cycles of escBEACOPP, but with significantly reduced toxicity.

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INTRODUCTION

The introduction of polychemotherapy regimens, consolidated when required with involved-field radiotherapy (IFRT), rendered Hodgkin lymphoma (HL) a highly curable disease. The most popular regimen used in HL is still ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine), with a 5-year progression-free survival (PFS) of 61% to 76% in patients with advanced stage of the disease.[1-5] The more intensive regimens, such as escalated BEACOPP (escBEACOPP: bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone), developed by the German Hodgkin Study Group (GHSG), improves the outcome of younger patients with advanced stages, allowing for a 5-year PFS of 90%.[6,7] However, 6 to 8 cycles of escBEACOPP result in significant hematological toxicity and late complications, such as secondary acute myeloid leukemia (AML), myelodysplastic syndrome (MDS), and infertility.[8-10]

The choice of the first-line chemotherapy regimen in HL is still a matter of controversy. It is crucial to maintain the balance between disease control and treatment-related adverse events (AEs). To avoid excess toxicity, risk-adapted strategies have been implemented. An early response assessment by ^{18}F-fluorodeoxyglucose positron emission tomography–computed tomography (PET-CT) performed after 2 cycles of chemotherapy (PET2) has become an accepted prognostic tool in classic HL. We postulated that early responders to escBEACOPP therapy (as assessed by PET2) may be further efficiently treated with ABVD regimen, with a decreased number of AEs and late complications.[11-13]

PATIENTS AND METHODS

Study cohort

In this retrospective analysis, we collected data from 188 consecutive, previously untreated patients with advanced HL (clinical stage III–IV or II with large tumor burden and concomitant general symptoms; IIBX–IV), who completed their entire treatment at the Department of Hematology at Jagiellonian University between April 2003 and August 2012. The diagnosis, established according to the 2001 or 2008 World Health Organization classification, was based on histopathological assessments of tissue samples excised before first-line therapy.[14,15] The clinical stage of lymphoma was assessed using the Ann Arbor classification with Cotswolds modification.[16] The International prognostic index (IPI) for HL was calculated for all patients at diagnosis.[17]

The median age at baseline was 33 years (range, 18–59 years) with a male-to-female ratio of 1.38. A total of 139 patients (73.9%) presented B symptoms, 119 (63.3%) had stage III or IV disease, and 69 (36.7%) had stage IIBX; 100 patients (53.2%) had an IPI of 3 or higher. Patient characteristics and demographic data are summarized in TABLE 1.

Treatment outline

Patients were referred for escBEACOPP therapy based on a physician's decision and their informed choice. The regimen was offered to all patients with stages IIBX to IV, good performance status (0–2) according to the Eastern Cooperative Oncology Group, and no disabling comorbidities. Patients over 60 years old were excluded, and only 16 patients (8.51%) were over 45 years old. All patients underwent a physical examination, full blood cell count, measurement of urea and electrolyte levels, liver function tests, and PET-CT at diagnosis. The first 2 cycles of escBEACOPP were followed by an early PET-CT response assessment (PET2). A complete response (CR) was initially defined as an inferior activity of involved tissues compared with mediastinal blood pool structures. In 2010, we switched to Deauville criteria which define CR as a PET score of 1 to 3.[18] In responding patients, the intensity of the therapy was decreased, and they were assigned to 4 cycles of ABVD regimen, while those with an active disease continued treatment with escBEACOPP for a total of 6 cycles. Chemotherapy regimens were administered in accordance with their original description.[19,20] The average relative dose intensity, calculated for all cycles of escBEACOPP and ABVD chemotherapy, was based on the patient's body surface area, planned and actually administered doses of drugs, and planned and actual dates of chemotherapy cycles. Consolidation IFRT with a total of 36 Gy was allowed for patients with stage IIBX.

The final response to first-line therapy was assessed in accordance with the original Cheson criteria[21,22] and the results of PET-CT performed within a month of chemotherapy completion or 3 months after consolidation IFRT.[18] Patients with partial remission (PR), stable disease, or progressive disease were regarded as treatment failure and, wherever possible, subjected to further salvage therapy and autologous stem cell transplantation (ASCT).

All patients received supportive treatment per local standard, including prevention of tumor lysis syndrome; antibacterial, antiviral, or antifungal therapy, and transfusions of red blood cells or platelets as required. Granulocyte colony-stimulating factor was regarded mandatory during escBEACOPP cycles as prophylaxis of neutropenic fever.

Follow-up visits were performed at 3-month intervals within the first year, every 6 months in the second year, and every 12 months until the end of the fifth year. After that time, patients were consulted whenever new signs or symptoms occurred. Computed tomography scans after therapy were performed at 6, 12, and 24 months; later, imaging studies were performed on individual basis, when appropriate. The survival data were updated in 2019, before drafting the manuscript, in additional visits or phone conversations.

Progression-free survival was defined as the time from onset of escBEACOPP chemotherapy to lymphoma progression or death. Overall survival was calculated as the time from the beginning of treatment to death, regardless of

TABLE 1 Patient characteristics and demographic data

Age, y, median (range)		33 (18–59)
Age	18–24 years	108 (57.4)
	25–44 years	64 (34)
	45–59 years	16 (8.51)
Male sex		109 (58)
ECOG performance status, median (range)		1 (0–2)
Histological subtype of lymphoma	Nodular sclerosis	142 (75.5)
	Mixed cellularity	3 (1.6)
	Lymphocyte rich	2 (1.1)
	Lymphocyte depleted	2 (1.1)
	Unclassified	39 (20.7)
Ann Arbor	IIBX	69 (36.7)
	III	45 (23.9)
	IV	74 (39.4)
Bulky disease		125 (66.5)
B symptoms		139 (73.9)
International prognostic index	0–2	88 (46.8)
	3–7	100 (53.2)

Data are presented as number (percentage) unless otherwise indicated.

Abbreviations: ECOG, Eastern Cooperative Oncology Group

the cause. Efficacy and survival analyses were performed separately in low- and high-risk groups (with an IPI of 0–2 and 3–7, respectively). Adverse events were assessed according to the Common Terminology Criteria for Adverse Events v2.0 from April 2003 to August 2006, v3.0 from September 2006 to May 2009, v4.0 from June 2009 to June 2010, and v4.03 from July 2010 to August 2012.[23]

The study was approved by the Bioethics Committee of Jagiellonian University (no., 1072.6120.59.2017). Patients provided written informed consent to participate in the study.

Statistical analysis Survival analysis (PFS and OS) was performed using Kaplan–Meier statistics with the log-rank test for comparison. Response rates were compared by the Pearson χ^2 test. The frequency of AEs was compared by the χ^2 test (including Yates correction). Results were considered significant at a P value of less than 0.05. All statistical analyses were performed using STATISTICA software (StatSoft, Kraków, Poland).

RESULTS In the whole cohort (n = 188), 161 patients achieved CR (85.6%) and 4 patients achieved PR (2.1%); 23 patients were regarded primary resistant (12.2%). At the median follow-up of 10.4 years (range, 1.3–18.4 years), the PFS and OS at 10 years were 79.3% and 89.4%, respectively, in the whole group (FIGURES 1 and 2, TABLE 2). Among all analyzed patients, 21 deaths occurred (16 in high-risk patients according to IPI, 13 high-risk cases according to PET2); 20 deaths were caused by HL and 1 death resulted from a traffic accident.

Early response assessment (PET2) performed after the second cycle confirmed CR in 141 patients (75%), which allowed for a decreased intensity of chemotherapy and switch from escBEACOPP to ABVD regimen. Consolidation with IFRT was applied in 64 patients (92.8% of those with stage IIBX). After completion of the entire first-line therapy in the PET2 responder cohort, ORR was 92.2%, including 129 patients (91.5%) with CR and 1 patient (0.7%) with PR. Eleven patients (7.8%) who achieved CR on PET2 assessment progressed while on ABVD and continued with salvage high-dose therapy. The majority of them (n = 9 [81.8%]) were successfully consolidated with ASCT, while 2 patients (18.2%) did not respond to salvage therapy and died (TABLE 2). At 10-year follow-up, PFS and OS in PET2 responders were 87.2% and 95%, respectively (FIGURES 3 and 4). Among the 47 patients with a PET2-positive scan who continued with 4 additional escBEACOPP cycles up to 6 courses, 35 (74.5%) responded to treatment with CR (32 patients [68.1%]) and PR (3 patients [6.4%]); 12 patients (25.5%) were primary refractory and subjected to high-dose therapy or ASCT, with the response observed only in 5 patients (41.7%). The inferior outcome in this group was confirmed by PFS and OS at 10-year follow-up (55.3% and 72.3%, respectively).

According to IPI stratification, in the low-risk group (IPI, 0–2; n = 88), 96.6% of patients completed the first-line treatment with CR; 1.1%, with PR; and 2.3% were primary refractory, with PFS and OS at 10 years of 93.2% and 94.3%, respectively. In the high-risk group (IPI, 3–7; n = 100), we observed CR in only 76% of patients and PR in 3%, while 21% of patients were primary refractory. In the high-risk group, PFS and OS at 10 years

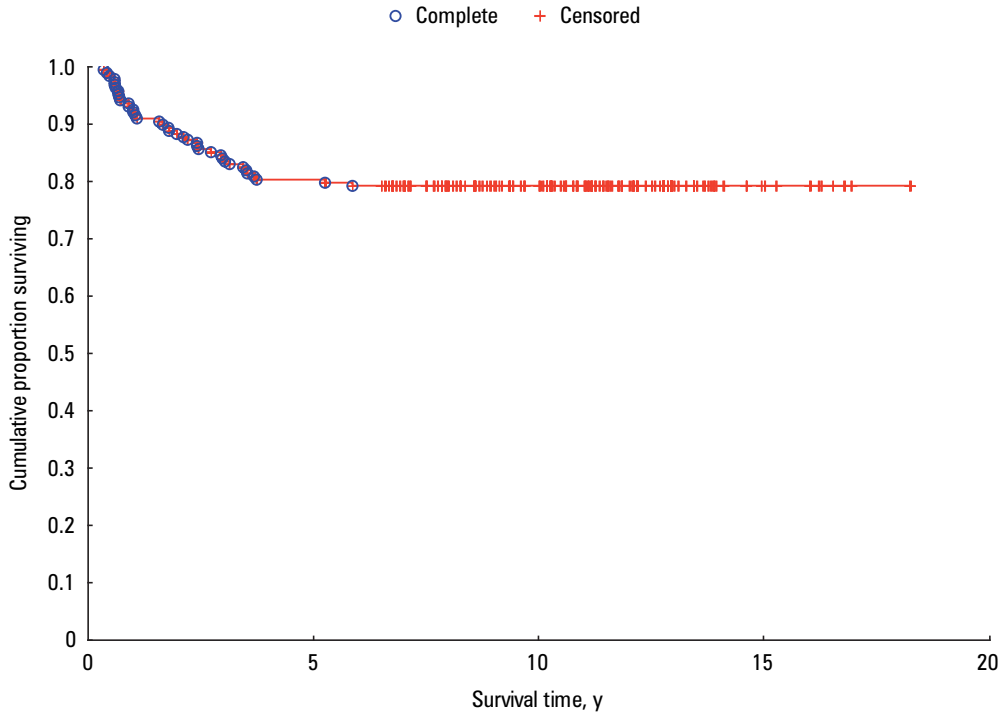

FIGURE 1 Progression-free survival analysis in the whole cohort (188 patients)

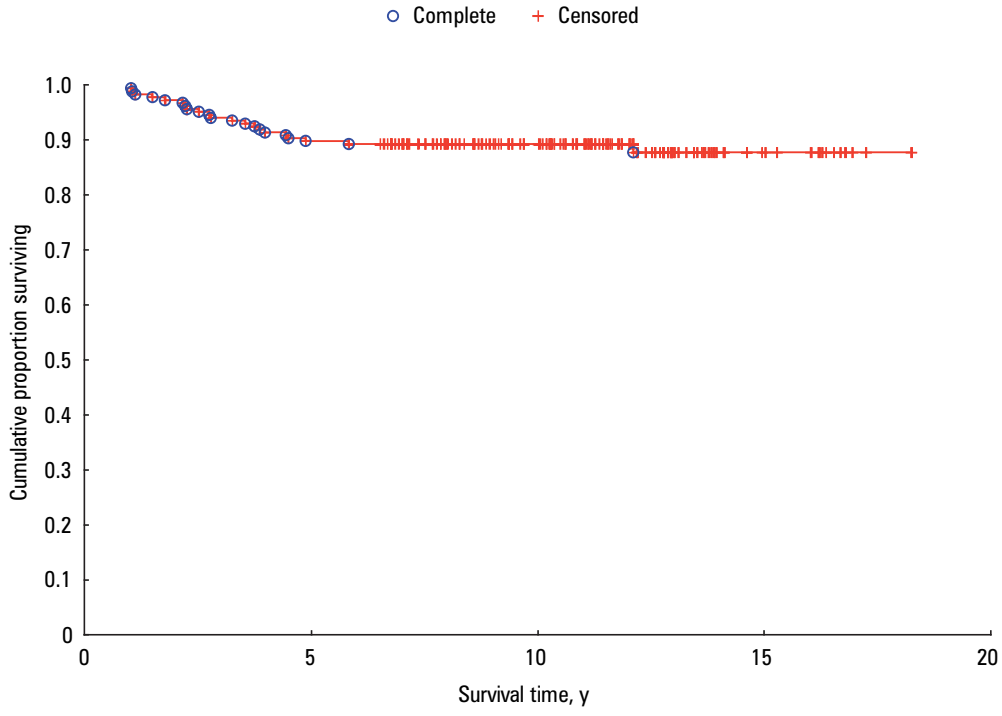

FIGURE 2 Overall survival analysis in the whole cohort (188 patients)

were 67% and 85%, respectively. Response rates to treatment according to the IPI and PET2 results are presented in TABLE 2.

The average relative dose intensity of escBEACOPP and ABVD regimens was 84% and 96%, respectively. The average relative dose intensity of the entire treatment was 91%, which was above the recently recommended 90% in lymphoma therapy.[24] Overall, 35 of the 188 patients (19%) required at least one dose reduction during treatment with escBEACOPP; in 29 cases, bleomycin and vincristine infusion was omitted on the eighth day of treatment because of neutropenia. In ABVD regimen, no chemotherapy dose adjustment was necessary due to neutropenia. The cumulative dose of doxorubicin was 270 mg/m^2 in the PET2-negative arm and 200 mg/m^2 in the PET2-positive arm. There were no episodes of early or late cardiotoxicity or treatment discontinuation in this group.

Adverse events of any grade occurred in 140 patients (74.5%). The most frequent AEs were neutropenia (grade 1–2, 56.9%; grade 3–4, 66%), anemia (grade 1–2, 83%; grade 3–4, 24.5%), thrombocytopenia (grade 1–2, 48.4%; grade 3–4, 12.2%), febrile neutropenia (no episodes of grade 1–2; grade 3–4, 17%). Serious AEs occurred in 26% of patients, with febrile neutropenia being the most

TABLE 2 Comparison of outcome in relationship to baseline international prognostic index or positron emission tomography results and chemotherapy de-escalation strategy

	All, n	CR, n (%)	PR, n (%)	SD + PD, n (%)	Relapse, n (%)	Mortality, n (%)	PFS at 10 years, %	OS at 10 years, %
IPI for HL								
Low-risk 0–2	88	85 (96.6)	1 (1.1)	2 (2.3)	4 (4.5)	5 (5.7)	93.2	94.3
High-risk ≥3	100	76 (76)	3 (3)	21 (21)	12 (12)	16 (16)	67	85
P value			<0.001		0.1	0.03	<0.001	0.03
Early response assessment by PET								
PET2 negative	141	129 (91.5)	1 (0.7)	11 (7.8)	7 (5)	8 (5.7)	87.2	95
PET2 positive	47	32 (68.1)	3 (6.4)	12 (25.5)	9 (19.1)	13 (27.7)	55.3	72.3
P value			<0.001		0.003	<0.001	<0.001	<0.001
Complete study cohort								
All patients	188	161 (85.6)	4 (2.1)	23 (12.2)	16 (8.5)	21 (11.2)	79.3	89.4

Abbreviations: CR, complete remission; IPI, International Prognostic Index; OS, overall survival; PD, progressive disease; PET2, positron emission tomography result after 2 cycles of chemotherapy; PFS, progression-free survival; PR, partial remission; SD, stable disease

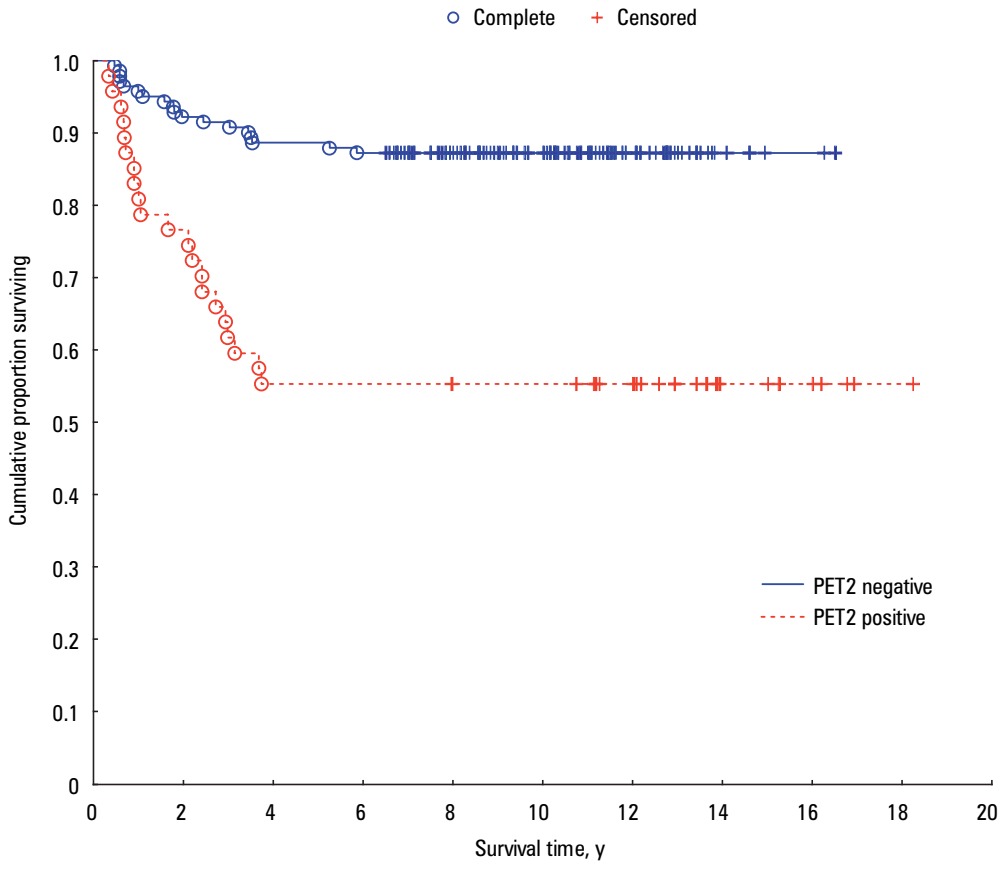

FIGURE 3 Progression-free survival analysis in relationship to positron emission tomography results and chemotherapy de-escalation strategy (log-rank test, *P* <0.001)

frequent one. Apart from hematological toxicity, the most common complications of grade 3 or 4 were thromboembolic events (exact pulmonary embolism) in 1.6% of patients. Hematological AEs and thromboembolic complications were significantly more frequent in patients treated with 6 escBEACOPP cycles (TABLE 3).

During the median follow-up of 10.4 years, we did not observe MDS or AML. The only secondary cancers reported were 4 cases of basal cell skin carcinoma and 2 cases of breast cancer, all in patients treated with 6 escBEACOPP cycles. There were no deaths related to AEs.

We did not formally assess fertility, but it should be noted that 48 pregnancies have been reported after completion of therapy (28 women and the wives of 20 male patients). Assisted reproduction was required in 5 cases, all treated with 6 cycles of escBEACOPP, 2 of them with consolidated IFRT, and 1 after ASCT.

DISCUSSION There are continuous efforts to develop an effective strategy with acceptable toxicity for patients with advanced-stage HL. PET-adapted strategies provide improved control of the disease without an increase in toxicity. In

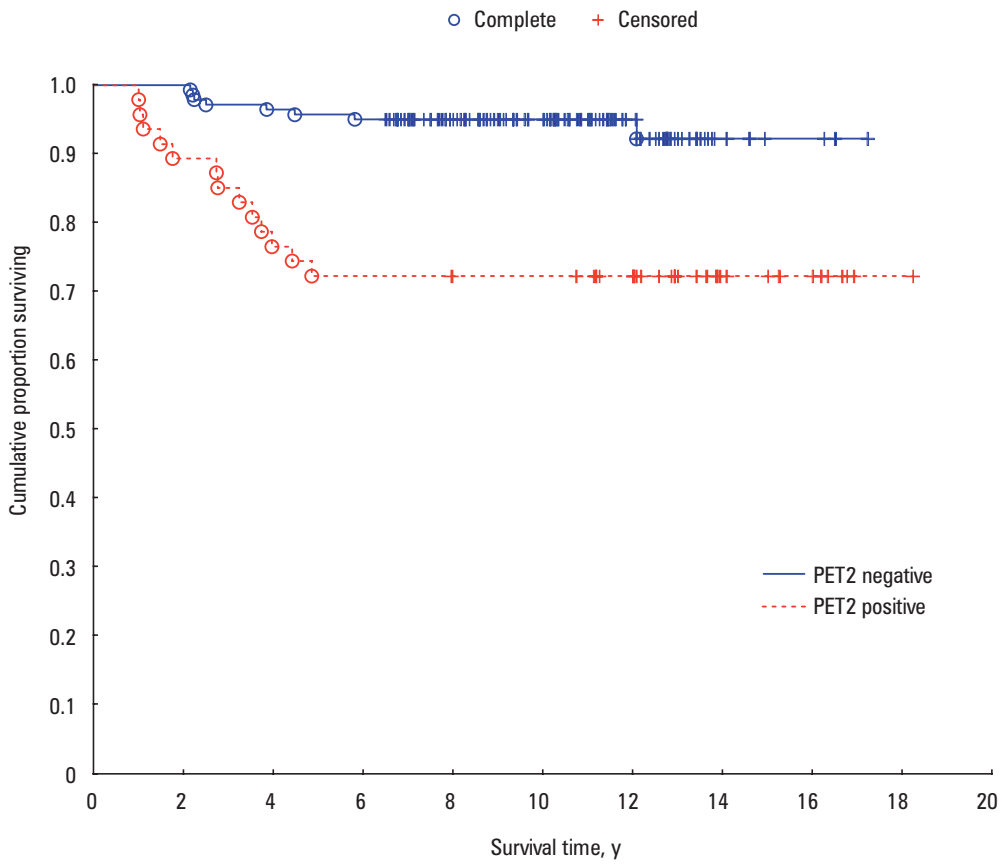

FIGURE 4 Overall survival analysis in relationship to positron emission tomography results and chemotherapy de-escalation strategy (log-rank test, $P < 0.001$)

patients treated with an upfront escBEACOPP regimen, the negative predictive value of PET2 for PFS was 98%.[11] We presented a de-escalation protocol guided by early PET-CT response assessment performed after the second cycle of escBEACOPP, which allowed a de-escalation to ABVD regimen in 75% of patients. A randomized comparison (AHL2011 [PET-adapted treatment for newly diagnosed advanced Hodgkin lymphoma] study) of 6 escBEACOPP cycles, regarded as a standard arm, with PET-driven de-escalation in patients responding to the first 2 cycles (2 × escBEACOPP followed by 4 × ABVD) showed equal efficacy and decreased toxicity between approaches.[13] Our protocol was identical to the experimental arm of the AHL2011 study; however, the median follow-up time was twice as long (10.4 vs 4.2 years). In the AHL2011 study, the projected 5-year PFS in the experimental arm was 85.7%. An increased risk of progression or relapse was associated with positive results in PET2 (5-year PFS in the PET2-negative group vs the PET2-positive group was 70.7% vs 88.9%, $P < 0.0001$).[13] A multivariable analysis proved that an early PET-CT assessment had a prognostic value independent of IPI.[13] In the AHL2011 study, the outcome of patients treated in the standard arm (6 cycles of escBEACOPP) was similar to that reported with the same regimen in the HD15 protocol of GHSG, comparing 8 and 6 cycles of escBEACOPP with 8 cycles of baseline BEACOPP 14 (PFS at 5 years was 90.3%).[7,13] Progression-free survival was also similar (91.4% at 3 years) for patients treated in the escBEACOPP arm according to the HD18 protocol, allowing for a shortened therapy in PET2 responders (4 × escBEACOPP) and adding rituximab in patients with an active disease on PET2 (2 × escBEACOPP + 6 × R-BEACOPP).[25] In our analysis, in the whole cohort, PFS and OS at 10 years were 83% and 90%, respectively. Although the PFS at 5 years was lower in our study than in the GHSG studies, a 10-year follow-up allowed us to demonstrate a durable benefit of less intensive treatment, with no relapses after 6 years. Our PET2-negative patients achieved even better results at 10 years (PFS, 87.2%; OS, 95%), without long-lasting complications.

Patients included in the analysis were treated before targeted therapies, such as anti-CD30 monoclonal antibodies (brentuximab vedotin [BV]), or checkpoint inhibitors were available. Originally approved for relapsing or refractory cases, BV has been recently tested in the first-line setting. In the ECHELON-1 study, 1334 treatment-naive patients with advanced HL were randomized to ABVD vs BV plus AVD (ABVD without bleomycin, which was substituted by BV).[26] At 2 years, modified PFS, the primary target of the study, in the BV-plus-AVD arm was 82.1%.[26] Adverse events were relatively frequent: 43% of the patients experienced serious AEs, 37% had to be hospitalized, and 67% developed long-lasting peripheral neuropathy.[26] Although a direct comparison with our results is not possible (there were more elderly patients

TABLE 3 Comparison of adverse event occurrence during chemotherapy

Adverse events[a]	All patients n = 188		Grade 1–2		*P* value	Grade 3–4		*P* value
	Grade 1–2, n (%)	Grade 3–4, n (%)	PET2-negative group (n = 141), n (%)	PET2-positive group (n = 47), n (%)		PET2--negative group (n = 141), n (%)	PET2-positive group (n = 47), n (%)	
Neutropenia	107 (56.9)	124 (66)	62 (44)	45 (95.7)	<0.001	82 (58.2)	42 (89.4)	0.002
Febrile neutropenia	0	32 (17)	0	0	–	7 (5)	25 (53.2)	<0.001
Anemia	156 (83)	46 (24.5)	124 (87.9)	32 (68.1)	0.002	11 (7.8)	35 (74.5)	<0.001
Thrombocytopenia	91 (48.4)	23 (12.2)	46 (32.6)	45 (95.7)	<0.001	7 (5)	16 (34)	<0.001
Sepsis	0	2 (1.1)	0	0	–	0	2 (4.3)	0.1
Pneumonia	9 (4.8)	0	2 (1.4)	7 (14.9)	<0.001	0	0	–
Peripheral neuropathy	38 (20.2)	0	20 (14.2)	18 (38.3)	<0.001	0	0	–
AST or ALT elevation	55 (29.3)	2 (1.1)	16 (11.3)	39 (83)	<0.001	1 (0.7)	1 (2.1)	1.0
Cardiotoxicity	0	0	0	0	–	0	0	–
Tumor lysis syndrome	0	0	0	0	–	0	0	–
Thromboembolic event	14 (7.4)	3 (1.6)	5 (3.5)	9 (19.1)	0.001	0	3 (6.4)	0.02
Vomiting	57 (30.3)	0	15 (10.6)	42 (89.4)	<0.001	0	0	–
Diarrhea	32 (17)	0	8 (5.7)	24 (51.1)	<0.001	0	0	–
Mucositis	46 (24.5)	1 (0.5)	11 (7.8)	35 (74.5)	<0.001	0	1 (2.1)	0.6

a Adverse events were assessed according to Common Terminology Criteria for Adverse Events (see the PATIENTS AND METHODS section).

Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase

in the ECHELON-1 study), BV in the first line is an alternative, not a breakthrough. Therefore, especially in countries with lower economic status, BV is unlikely to become the new standard of care in the first-line therapy.

Of note, we observed 11 patients (7.8%) with negative PET2 results to progress while on ABVD therapy (1 low-risk patient and 10 high-risk patients according to IPI); thus, although early PET2 assessment remains a predictor of good prognosis, it cannot serve as a surrogate of CR. We observed 12 primary-resistant cases (25.5%) in the PET2-positive group; further intensive therapy resulted in a 10-year PFS and OS of 55.3% and 72.3%, respectively.

In our early de-escalation strategy, IPI remained an important prognostic factor for both PFS and OS. High-risk patients according to IPI, when compared with low-risk patients, had a lower response rate (CR, 96.6% vs 76%) and higher relapse rate (4.5% vs 12%). Both low IPI and good clinical response on PET2 assessment allowed us to identify a favorable prognostic subgroup in patients with advanced HL, with an OS of 94% to 95% at 10 years. However, IPI for HL allowed us to identify only 88 cases (46%) belonging to a favorable prognostic subgroup, while an early PET assessment doubled this number to 141 patients (75%). Therefore, our data strongly suggest that PET2 is a better tool to identify low-risk patients.

In our analysis, we observed lower rates of AEs, elimination of bleomycin-related pulmonary toxicity, as well as no secondary solid tumors, MDS, or AML. Toxicity in PET2-negative patients de-escalated to ABVD in the AHL2011 study was comparable to our results and lower than in patients treated with 4 cycles of escBEACOPP in the HD18 study.[13,25] There were fewer cases of anemia (grade ≥3) (24% vs 39%) and thrombocytopenia (36% vs 57%), similar rates of leukopenia (including febrile neutropenia), and bleomycin-related pulmonary toxicity was not observed.[25] Additionally, in the GHSG HD9 study,[6] after the median follow-up of 9.25 years, in the arm treated with 8 cycles of escBEACOPP, an increased incidence of secondary malignancies was reported (overall, 6%, including 3% for AML and 1.9% for solid tumors).[6]

The identified 9% rate of thromboembolic events prompts questions as to how the optimal primary thromboprophylaxis should be defined, especially in patients treated with escBEACOPP.[27] Overt cardiotoxicity was not observed in our study, which makes a significant difference in comparison with patients with non–Hodgkin lymphoma, who are older and more likely to have cardiovascular comorbidities.[28]

The principal aim of our study was to determine in a real-life setting whether an interim PET-CT–guided de-escalation strategy will maintain its high efficiency and reduce the number of AEs and late complications. The single-center, retrospective analysis has several limitations, including the possibility of an involuntary patient selection and the lack of an independent PET-CT assessment. However, the long median follow-up duration, exceeding 10 years, relatively low

therapy-related toxicity, and the exceptionally good PFS and OS remain the meaningful value of our analysis.

In summary, the early PET-driven strategy allowed for de-escalation of upfront escBEACOPP regimen in 75% of patients with advanced-stage HL and improved tolerability of therapy without impairing its long-term results.

ARTICLE INFORMATION

CONTRIBUTION STATEMENT MD-D, SS, BM, AS-S, and WJ performed the study and analyzed the data. WJ designed the study. MD-D, WJ, BM, and SS had substantial contributions to conception and design of the study. MD-D, SS, PK, and WJ drafted the manuscript. MD-D, SS, JK, and WJ critically revised the manuscript for important intellectual content. MD-D, SS, WJ, AK, PK, AG, DZC, BM, AS-S, and JK contributed substantially to the acquisition, analysis, and interpretation of data for the study. The authors had full access to the data and take full responsibility for data integrity. All authors have read and agreed with the content of the manuscript.

CONFLICT OF INTEREST None declared.

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REFERENCES

1 Canellos GP, Anderson JR, Propert KJ, et al. Chemotherapy of advanced Hodgkin's disease with MOPP, ABVD, or MOPP alternating with ABVD. N Engl J Med. 1992; 327: 1478-1484.

2 Duggan DB, Petroni GR, Johnson JL, et al. Randomized comparison of ABVD and MOPP/ABV hybrid for the treatment of advanced Hodgkin's disease: report of an intergroup trial. J Clin Oncol. 2003; 21: 607-614.

3 Gordon LI, Hong F, Fisher RI, et al. Randomized phase III trial of ABVD versus Stanford V with or without radiation therapy in locally extensive and advanced-stage Hodgkin lymphoma: an intergroup study coordinated by the Eastern Cooperative Oncology Group (E2496). J Clin Oncol. 2013; 31: 684-691.

4 Hoskin PJ, Lowry L, Horwich A, et al. Randomized comparison of the Stanford V regimen and ABVD in the treatment of advanced Hodgkin's Lymphoma: United Kingdom National Cancer Research Institute Lymphoma Group Study ISRCTN 64 141 244. J Clin Oncol. 2009; 27: 5390-5396.

5 Bonfante V, Santoro A, Viviani S, et al. ABVD in the treatment of Hodgkin's disease. Semin Oncol. 1992; 19: 38-44.

6 Engert A, Diehl V, Franklin J, et al. Escalated-dose BEACOPP in the treatment of patients with advanced-stage Hodgkin's lymphoma: 10 years of follow-up of the GHSG HD9 study. J Clin Oncol. 2009; 27: 4548-4554.

7 Engert A, Haverkamp H, Kobe C, et al. Reduced-intensity chemotherapy and PET-guided radiotherapy in patients with advanced stage Hodgkin's lymphoma (HD15 trial): a randomised, open-label, phase 3 non-inferiority trial. Lancet. 2012; 379: 1791-1799.

8 Josting A, Wiedenmann S, Franklin J, et al. Secondary myeloid leukemia and myelodysplastic syndromes in patients treated for Hodgkin's disease: a report from the German Hodgkin's Lymphoma Study Group. J Clin Oncol. 2003; 21: 3440-3446.

9 Behringer K, Breuer K, Reineke T, et al. Secondary amenorrhea after Hodgkin's lymphoma is influenced by age at treatment, stage of disease, chemotherapy regimen, and the use of oral contraceptives during therapy: a report from the German Hodgkin's Lymphoma Study Group. J Clin Oncol. 2005; 23: 7555-7564.

10 Behringer K, Mueller H, Goergen H, et al. Gonadal function and fertility in survivors after Hodgkin lymphoma treatment within the German Hodgkin Study Group HD13 to HD15 trials. J Clin Oncol. 2013; 31: 231-239.

11 Dann EJ, Bar-Shalom R, Tamir A, et al. Risk-adapted BEACOPP regimen can reduce the cumulative dose of chemotherapy for standard and high-risk Hodgkin lymphoma with no impairment of outcome. Blood. 2007; 109: 905-909.

12 Avigdor A, Bulvik S, Levi I, et al. Two cycles of escalated BEACOPP followed by four cycles of ABVD utilizing early-interim PET/CT scan is an effective regimen for advanced high-risk Hodgkin's lymphoma. Ann Oncol. 2010; 21: 126-132.

13 Casasnovas RO, Bouabdallah R, Brice P, et al. PET-adapted treatment for newly diagnosed advanced Hodgkin lymphoma (AHL2011): a randomised, multicentre, non-inferiority, phase 3 study. Lancet Oncol. 2019; 20: 202-215.

14 Pathology and genetics of tumours of haematopoietic and lymphoid tissues. In Jaffe E, Harris N, Stein H, et al, eds. World Health Organization Classification of Tumors. Lyon, France: IARC Press; 2001.

15 Campo E, Swerdlow SH, Harris NL, et al. The 2008 WHO classification of lymphoid neoplasms and beyond: evolving concepts and practical applications. Blood. 2011; 117: 5019-5032.

16 Carbone PP, Kaplan HS, Musshoff K, et al. Report of the Committee on Hodgkin's Disease Staging Classification. Cancer Res. 1971; 31: 1860-1861.

17 Hasenclever D, Diehl V. A prognostic score for advanced Hodgkin's disease. International Prognostic Factors Project on Advanced Hodgkin's Disease. N Engl J Med. 1998; 339: 1506-1514.

18 Barrington SF, Qian W, Somer EJ, et al. Concordance between four European centres of PET reporting criteria designed for use in multicentre trials in Hodgkin lymphoma. Eur J Nucl Med Mol Imaging. 2010; 37: 1824-1833.

19 Diehl V, Franklin J, Pfreundschuh M, et al. Standard and increased-dose BEACOPP chemotherapy compared with COPP-ABVD for advanced Hodgkin's disease. N Engl J Med. 2003; 348: 2386-2395.

20 Bonadonna G, Zucali R, Monfardini S, et al. Combination chemotherapy of Hodgkin's disease with adriamycin, bleomycin, vinblastine, and imidazole carboxamide versus MOPP. Cancer. 1975; 36: 252-259.

21 Cheson BD, Horning SJ, Coiffier B, et al. Report of an international workshop to standardize response criteria for non-Hodgkin's lymphomas. NCI Sponsored International Working Group. J Clin Oncol. 1999; 17: 1244.

22 Cheson BD, Pfistner B, Juweid ME, et al. Revised response criteria for malignant lymphoma. J Clin Oncol. 2007; 25: 579-586.

23 NCI guidelines for investigators: adverse event reporting requirements for DCTD (CTEP and CIP) and DCP INDs and IDEs. Bethesda, MD, USA: National Cancer Institute; 2012. Accessed March 1, 2019.

24 Dlugosz-Danecka M, Szmit S, Ogorka T, et al. The average relative dose intensity of R-CHOP is an independent factor determining favorable overall survival in diffuse large B-cell lymphoma patients. Cancer Med. 2019; 8: 1103-1109.

25 Borchmann P, Haverkamp H, Lohri A, et al. Progression-free survival of early interim PET-positive patients with advanced stage Hodgkin's lymphoma treated with BEACOPPescalated alone or in combination with rituximab (HD18): an open-label, international, randomised phase 3 study by the German Hodgkin Study Group. Lancet Oncol. 2017; 18: 454-463.

26 Connors JM, Jurczak W, Straus DJ, et al. Brentuximab Vedotin with Chemotherapy for Stage III or IV Hodgkin's Lymphoma. N Engl J Med. 2018; 378: 331-344.

27 Zamorano JL, Lancellotti P, Rodriguez Munoz D, et al. 2016 ESC Position Paper on cancer treatments and cardiovascular toxicity developed under the auspices of the ESC Committee for Practice Guidelines: The Task Force for cancer treatments and cardiovascular toxicity of the European Society of Cardiology (ESC). Eur Heart J. 2016; 37: 2768-2801.

28 Szmit S, Jurczak W, Zaucha JM, et al. Acute decompensated heart failure as a reason of premature chemotherapy discontinuation may be independent of a lifetime doxorubicin dose in lymphoma patients with cardiovascular disorders. Int J Cardiol. 2017; 235: 147-153.